Recommendation for a Collaborative Centre of Expertise for Rare Diseases in Northern Ireland (CERDNI)

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Collectively, rare diseases represent a significant public health burden for both affected families and health and social care services. Rare diseases should be a key priority for healthcare providers within Northern Ireland. A rare disease is defined by the European Union as one that affects less than 5 in 10,000 of the general population with ~8,000 rare diseases recorded. $^{1}/_{17}$ individuals are affected by a rare disease, which equates to more than 100,000 individuals (a similar number to the population of Derry/Londonderry) in Northern Ireland. Individuals, carers and families who are affected by rare disease are protected by equality legislation and human rights standards, and are therefore entitled to the same level of care and support as those who are affected by more common conditions. In essence what this means is that patients with a rare disease (and their families) expect to have access to services provided by professionals who understand their condition and have access to the appropriate medical tools and devices to manage their condition effectively.

It is not feasible for the Northern Ireland health service to provide "in house" experts for all rare diseases. Northern Ireland has a relatively small population and as a result, for many rare disease, we do not have the critical mass of affected individuals to allow clinicians to develop the expertise that would allow them to satisfactorily manage their care. The provision of a local specialist service for very small numbers of patients for all individual rare diseases is not economically viable.

Nonetheless, the present care of patients with rare diseases is not as efficient or streamlined as possible. The waste of misdirected NHS resources is immense. The Northern Ireland Rare Disease Partnership (NIRDP) considers that the issues involved - of needless human suffering and of waste of public money - demand that workable solutions are found. Ideally we envisage the CERDNI as a productive, collaborative endeavour as we have already established strong academic - clinical - government – industrial - voluntary sector links through evaluating the logistics of how a NI centre of expertise for rare diseases could be most effective. This represents an innovative solution to the challenges of improving the plan for rare disease, reducing expenditure on referrals outside NI, and improving quality of service and outcomes for those with rare disease, might be to work towards the establishment of a Northern Ireland Rare Disease "Centre of Expertise". We believe that NI already has a range of experts with relevant expertise and is ideally suited to the creation of such a centre, which would benefit:

- ✓ **Patients and carers** by providing access to standardised information to help them understand what to expect with their rare disease (the 'patient journey'), helpful guides to empower those affected, links to relevant support networks and voluntary groups. Ideally this CERDNI will help generate standardised care guidelines to optimise diagnosis, treatments and quality of life as well as translating promising research results into clinically relevant treatments.

- ✓ **Clinicians** by providing access to accredited standards of care guidelines, linking to relevant sources of professional information, and helping generate validated clinical

outcome measurements for rare diseases. Training and education would also be facilitated through the expert network of healthcare professionals.

- ✓ **Healthcare providers** by generating (or linking to existing) natural histories aiding strategic service planning and commissioning of relevant services

Researchers by contributing to well-designed natural history studies to help understand that aetiology and progression of rare diseases. To help validate relevant clinical outcomes, identify biomarkers, aid the development of potential therapies, and recruiting patients to clinical trials. The enhanced embedding of research in health service delivery will enable faster uptake of evidence-based best care, thereby improving the health of the population affected by a rare disease in Northern Ireland. Industrial partnerships will maximise translational medicine through new drug targets, biomarkers and clinical trials/practice. Rare disease efforts are currently supported by international pharmaceutical partners and Northern Ireland has a significant and growing pharmaceutical, diagnostic and biotechnology industry that offers NI substantial potential to prepare us for the future challenges of rare disease research and service delivery.

We are keen that CERDNI is of maximum benefit to individuals in NI living with a rare disease, as well as the professional clinicians, support team, commissioners and policy makers. Ideally there would be an advisory group comprising active stakeholders to ensure a long-term, sustainable resource that meets the needs of individuals living in Northern Ireland. The School of Medicine, Dentistry and Biomedical Sciences at Queen's University has invested more than £90 million in research infrastructure, buildings, equipment and facilities, with a further £85 million expenditure anticipated over the course of the next five years, to create a world class Institute of Health Sciences and Health Sciences Campus. The University of Ulster has recently established a new £11.5M Northern Ireland Centre for Stratified (Personalised) Medicine and is committed to its development as an area of excellence. ***We envisage five essential components of CERDNI including:***

1. **Multidisciplinary Clinics:** Rare disease networks and multidisciplinary teams are often vital to improve patient's lives. The communications infrastructure and network of professionals (including expert patients) resourced by a comprehensive multidisciplinary clinical cannot be underestimated. As an excellent European example of good practice, the Treat-NMD network for neuromuscular diseases (http://www.treat-nmd.eu) was established in 2007 and now has 22 interested partners covering 11 countries with more than 300 collaborators worldwide.

In Northern Ireland, there have been recent developments for patients affected by Neuromuscular diseases, including the development of a patient journey that has a commitment to be piloted by all Trusts in the local commissioning plan 2013/2014. The South West of England Neuromuscular Network has demonstrated the improvements that can be made to specialist care if services are linked together in an effective and efficient way. The Network is overseen by a group of NHS, patient representatives and health professionals such as Neuromuscular Care Advisors to help co-ordinate service provision for patients with complex neuromuscular conditions and their families. Specialist care and support must to be provided at the right times throughout the lives of patients. This includes during the period of diagnosis and throughout the progression of rare conditions, when proper management is required. 'Anticipatory care' - planning ahead when it comes to thinking about specialist equipment and other interventions – is vital not only to improve lives, but to reduce costs as

well. There is a clear cut financial argument for this proactive approach – a recent NHS audit found 40 percent of the emergency admissions to hospital for neuromuscular patients could have been prevented through appropriate care. Multidisciplinary teams at 'Centres of Excellence' for muscular dystrophy and related conditions, such as Newcastle's Centre for Life, Great Ormond Street Children's Hospital in London and the John Radcliffe in Oxford, are well prepared for this approach. At such Centres, families can access specialist support from expert consultants and health professionals, which may include diagnostics, ongoing physiotherapy and integrated cardiac and respiratory services. By establishing links with community based teams through a formal network; additional health professionals can gain skills with more in depth knowledge of very rare conditions.

A multidisciplinary model has already proven successful for some rare diseases in Northern Ireland. Additionally, a specialist multidisciplinary clinic runs for patients affected by Fabry disease in NI to the same management guidelines as specialist centres in England. For some individuals affected by some other lysosomal storage disorders, expert consultants travel to Northern Ireland, while other patients attend designated centres in England. Patients referred to an expert centre outside Northern Ireland will often need to be accompanied by a carer, family member or friend; thus increasing the cost of such trips. It is also important to realise that individuals with a rare disease are only one part of their family. Families will often have other children and will have commitments close to home that make travelling to and from specialist centres very difficult. Coordinated care between specialist centres and local services: individuals affected by a rare disease may receive their specialist care outside of Northern Ireland but they are much more likely to develop complications, have accidents that require A&E visits, and pick up minor illnesses when they are at home; it is essential that local teams develop close links with specialist centres.

The opportunity to avail of such expert specialist knowledge should be equitably available to all individuals in NI living with a rare condition by in person visits, travel to expert centres (although some individuals may not be well enough to travel) or interactive telemedicine links.

2. Improved Diagnosis and Patient Journey.

Early interventions substantially improve the quality and life expectancy for affected individuals, but a recent survey showed ~30% of individuals waited 1-5 years for an accurate diagnosis with some individuals waiting more than ten years. Many individuals see more than 10 doctors and UK studies suggest that up to 40% of costs could be saved with improved preventative care minimising the number of unplanned hospital admissions. At least 80 per cent of rare diseases have a genetic origin.

Northern Ireland has a single regional genetics centre through which all tests are processed. This centre has integrated clinical diagnostics, geneticists and NHS-QUB research staff for more than 40 years. The national plan for rare diseases places a strong focus on genetics and technological advantages mean that many current 'common' conditions are being separated into many subtypes. The decreasing costs of next generation sequencing are enabling transformative approaches for rare disease research and NI is ideally suited to conduct a range of research projects with standardised, automated comprehensive next generation sequencing as well as improving quality control and effective verification of novel markers that may contribute to diagnostic pathways. Several publications support the use of next generation diagnostics for cost-effective diagnostic use, resources such as Addenbrookes hospital are developing a number of next generation sequencing services that will soon be offered for

clinical diagnostic use (http://www.cuh.org.uk/addenbrookes/services/clinical/genetics/genetics_labs/news/next_generation_sequencing.html) and the UK genetic testing network has evaluated several panels that minimise clinicians wasting time and delayed patient diagnosis by having to order each single test sequentially. The developments of these tests not only improve patient's experience of diagnosis, but often inform on the disease course, minimise invasive tests, and save costs! A case study of glycogen storage disorder using a targeted next generation sequencing approach enables a saving of £237,405 per annum and leads to definitive diagnostic testing based on the expected number of 70 referrals per annum for the UK population (Dr Shehla Mohammed, Clinical Advisor, UK Genetic Testing Network, which advises the NHS on genetic testing across the UK, in the 3rd Annual report, Nov 2012).

Northern Ireland's Centre for Public Health (QUB) and the Regional Genetics Centre (BHSCT) already acts as the European centre for multiple genetic and epigenetic studies for a range of diseases with extensive experience storing and analysing complex biological samples, including next generation sequencing and clinical bioinformatics.

For rare diseases without a genetic cause, the process of diagnosis may also be challenging due to infections, allergies, degenerative causes etc. Often patients will have multiple complications, see many consultants and attend lots of different clinics on different days. Where possible, care should be coordinated into a 'multi-stop-clinic' attended by a multidisciplinary team that will maximise patient attendance, facilitate cross-disciplinary expertise and minimise patients having inappropriate care. The development of patient journeys that help each patient understand what to expect at key stages of their disease progression will help minimise patient anxiety and empower affected individuals to make informed choices about their care and lifestyles.

3. **Clinical Trials and Orphan Drugs.** It is vitally important that local individuals are able to access clinical trials and funding for orphan drugs as other patients in the UK. Improved professional support is also required to facilitate local individuals participating in clinical trials; at present some individuals in NI cannot contribute to clinical trials as they do not have sufficient follow-up care through routine appointments. This is particularly disappointing given the development of the new Wellcome Trust-Wolfson Northern Ireland Clinical Research Facility, the NI Cancer Trials Centre, and the Medical Research Council Methodology Hub. Established links with pharmaceutical companies would enhance the research and translational hub and potentially benefit the economy.

4. **Streamlined cross-border commissioning facilitating access to relevant international specialist centres for rare diseases:** At present, some individuals from NI are waiting prolonged periods of time to access specialist care for their conditions in Europe. Once approved, difficulties are still experienced on arrival at their specialist centre and the existing language barriers that cause difficulties accessing care and translating medical notes need resolved.

5. **Information Hub:** A dedicated information hub for rare diseases is a powerful tool for surveillance, epidemiology, service planning, and would minimise costs, facilitate delivery of the national plan, and maximise Northern Ireland's ability to contribute to leading research for rare diseases. The development of this information hub would standardise data

collection and storage with a single entry point for access, maintain agreed core information sets for rare diseases in line with European policy, enable efficient accurate data validation, active updating, routine auditing, and integration with international registries. This would also minimise organisational / IT complexities integrating multiple information structures, and ensure compliance with data protection, quality assurance, governance and standardise legal issues including acting as a 'consent' centre for patient participation and the central portal for relevant clinical trials. Ideally primary data would be automatically derived from electronic healthcare records with extensive curation and validation, as well as having the facility to allow collection of data directly reported by patients and healthcare professionals. Such collation of data would also ensure that relevant medical information (patient history, disease information guidelines and contact details for further information) is available in a timely and appropriate manner when a patient with a rare disease presents at A&E in crisis. NI's electronic care record has already proved transformational and it is possible that a 'front page' of key/critical information would maximise patient outcomes during acute hospital admissions; we understand this 'alert' system for the ECR may be operational within 6 months. CERDNI would also enable the integration of resources such as a rare disease clinical registry with research-based next generation sequencing, metabolomic, proteomic and imaging data to improve clinical risk provision by identifying biomarkers for disease and optimising treatment.

An example of a UK-wide resource: The UK renal community has collectively contributed to the establishment of a Renal Registry (www.renalreg.com) that brings together rich clinical data under a careful confidentiality and governance framework; there is 100% participation from renal units across the UK and the 16th annual report is being generated. Patients are provided with access to up-to-date data for their medical condition via renal patient view (www.renalpatientview.org) and are thus able to contribute and share important information with relevant professionals anywhere in the world. This resource provides informative, standardised and validated data for comparative analyses, quality assurance, auditing, service planning, clinical governance and research for participating units, NHS Trusts, and commissioning authorities. Specific to rare renal diseases is a dedicated developing website (rarerenal.org) that provides information for clinicians, information for patients and their carers in accordance with the Information Standard, as well as providing information on National Studies of Rare Kidney Diseases. The latter includes the national patient registry renal_RaDaR that serves patients with over 25 rare conditions. This resource also provides the opportunity for epidemiological surveillance and identifies patients with rare renal diseases who may benefit from / contribute to clinical trials. Nationally approved expert rare renal disease groups provide detailed information and advice on tests, treatment and research; these groups must fulfil clear objectives to maintain approval by the professional organisation the Renal Association (www.renal.org), and contain patient representation as well as worldwide expertise from disciplines outside renal medicine.

a. **Registries:** Due to the rarity of patients and the scarcity of information related to individual rare diseases, collaborative endeavours are necessary, indeed the EU Council Recommendation on Rare Diseases and the EU Parliament and Council Directive on Cross-Border Health Care emphasises the need and urgency for cooperation among Countries in collecting and sharing data to foster research and care regarding patients living with rare diseases. This information should be used to support policy development, facilitate clinical and epidemiological research, therapeutic monitoring and evaluation of on/off label approved drug use, as well as facilitating clinical trials.

Northern Ireland currently coordinates the central registry for a network of population-based resources for congenital anomalies (www.eurocat-network.eu/), despite NI not contributing data from affected individuals directly. This established network uses a standardised protocol to collect data, surveying more than 1.7 million births per year in Europe, with 43 registries in 23 countries at European level. The EUROCAT Coding and Classification Committee are also currently liaising with the WHO, Orphanet and EURCERD in the revision of the Developmental Anomalies chapter of the new ICD 11 to develop to coding of congenital anomalies and other Rare Diseases. EUROCAT have also developed recommendations on policies to be considered for the primary prevention of congenital anomalies in National Plans (and strategies) on Rare Diseases. (http://www.eurocat-network.eu/content/EUROCAT-EUROPLAN-Primary-Preventions-Recommendations.pdf).

Northern Ireland also hosts many other successful resources, including the Cancer Registry (http://www.qub.ac.uk/research-centres/nicr/), cerebral palsy register (http://www.qub.ac.uk/research-centres/nicpr), Northern Ireland Childhood Diabetes Register, the European collaboration of childhood diabetes registers is co-ordinated from NI (EURODIAB, established 1989), the current chair of the UK Renal Registry is based in Northern Ireland (www.renalreg.com), a database of all individuals receiving a kidney transplant with up to 40+ years of comprehensive follow-up data, several long-term followup studies most recently NICOLA (Northern Ireland COhort for the Longitudinal study of Aging), and the Northern Ireland Barrett's Oesophagus Register has resulted in changes to clinical practice that minimise costs to healthcare providers and patients.

To be of maximum value to individuals and their families, health and social care providers, and local policy makers it is important that a regional population based registry of rare diseases in Northern Ireland is developed. Such a population based registry is essential for Northern Ireland and is timely with the recommendations on Rare Diseases Registry's and Data Collection which have just recently been released by EURCERD (http://www.eucerd.eu/wp-content/uploads/2013/06/EUCERD_Recommendations_RDRegistryDataCollection_adopted.pdf)

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b. **Web-based portals** for disseminating information to patients and healthcare professionals.

Due to the nature of rare diseases there are also very significant issues relating to both missed-diagnosis and misdiagnosis. There is an urgent need to improve awareness and educate medical professionals by providing 'diagnostic signposts' to ensure that service providers at primary and secondary care level are educated to consider the possibility of rare disease. It is also essential that medical professionals know how to appropriately refer patients for ongoing care. For many conditions it is possible to carry out initial tests locally. If initial test are carried out locally this can cut down the costs associated with potentially inappropriate referrals to recognised specialist centres outside Northern Ireland. This online resource could facilitate a "Virtual Clinical Team" led by clinicians across medical specialities, associated healthcare professionals, service providers. The web-based portal would enable access to appropriate, updated information from Centres of Excellence for all rare diseases, by forming the nucleus of a networking system: assimilating high quality advice, improving diagnostics and coordination of care. This resource would provide a network of support for local professionals and empower those professionals to manage a small number of patients with rare disease(s).

We believe the creation of the NIRDP and the generation of this draft plan with community stakeholders shows the dedication and commitment of a diverse range of individuals in Northern Ireland to ensure Northern Ireland is well placed to capitalise on rare disease developments. Our unique distribution of services and datasets, including a combined Health and Personal Social Services, central population-wide collation of electronic prescriptions [EPD the Enhanced Prescribing Database] and the inclusion of the Health and Care Number (HCN) as a unique identifier in healthcare datasets, offers unparalleled potential for fully integrated population based research in Northern Ireland. The collation of datasets in a central data warehouse accessed via the honest broker initiative facilitates the safe linkage of sensitive datasets and supports the analysis of datasets within secure / 'safe haven' locations. Making better use of information to help planning and delivering of healthcare for individuals affected by rare diseases is a critical development for Northern Ireland in particular. The launch of the Northern Ireland Electronic Health Record and the focus on personalised medicine in within the Transforming Your Care process, as well as the development of UK and NI implementation plan for rare disease make this a particularly timely endeavour. Health Minister Poots & Minister White (Primary Care at the DOH, ROI) both spoke at local rare disease conferences earlier this year, as did vice presidents from EURODIS, EU Committee of Experts on Rare Diseases, and John Rowan from the European Commission, Healthcare Systems Unit, SANCO D2.

This report recommends Northern Ireland develops a collaborative Centre of Expertise for Rare Disease (CERDNI), incorporating genetic diagnostics, a rare disease registry / electronic linkage of health records, and implementing the NIRD plan with evidence-based commissioning and translational research that changes lives.